Journal of Medical Virology 52:215–218 (1997)

Safety and Immunogenicity of Inactivated Hepatitis A Vaccine in Patients With Chronic Liver Disease

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The safety and immunogenicity of inactivated hepatitis A vaccine was evaluated in patients with chronic liver disease. Sixty hepatitis A virus antibody (anti-HAV) seronegative patients with chronic liver disease (56 chronic hepatitis B and four chronic hepatitis C) and from 17 to 47 years of age received a dose of 1440 ELISA units of the inactivated hepatitis A vaccine at month 0, and a booster at month 6. Anti-HAV seroconversion (≥33 mIU/mL) was 57.6% (34/59) on day 15, and reached 93.2% (55/59) 1 month after primary vaccination. At month 6, the seropositivity of anti-HAV decreased before the booster to 69.0% (40/58). All vaccinees had measurable titers of anti-HAV 1 month after booster vaccination, and were still seropositive at month 12. After initial vaccination, the geometric mean titers of anti-HAV among vaccine responders were 158, 264, 74, 1309, and 409 mIU/ml at day 15 and months 1, 6, 7, and 12. Overall, 59.7% (71/119) of the vaccine doses administered were followed by mostly minor reactions. The majority of symptoms reported were local, all of which resolved within 3 days after vaccination. No significant changes in serum liver enzyme levels were detected after vaccination. Thus, an inactivated hepatitis A vaccine was safe in patients with chronic liver disease while the immune response was inferior to that observed in healthy subjects reported in a previous study. ***J. Med. Virol. 52:215–218, 1997.***

KEY WORDS: inactivated hepatitis A vaccine; viral hepatitis; chronic liver disease

INTRODUCTION

While hepatitis A infection rarely results in death, mortality is age-dependent [Hadler, 1991], suggesting that cofactors may have a role in disease expression. Anecdotal reports suggest that hepatitis A may be more severe in persons with underlying liver disease. Some reports suggest that hepatitis A superimposed on chronic hepatitis B or other chronic liver diseases is associated with higher peak laboratory test abnormalities, more severe disease, including fulminant hepatic failure, and a higher fatality rate [Akriviadis and Redeker, 1989; Wang et al., 1986; Yao, 1991]. In the 1988 Shanghai epidemic of hepatitis A, over 300,000 cases and 47 deaths occurred. Fifteen of these deaths were caused by hepatitis A superimposed on chronic hepatitis B [Yao, 1991]. As shown in studies of patients with hepatitis B, various viruses and other cofactors may interact to cause severe or fulminant hepatitis [Feray et al., 1993; Wu et al., 1994].

Chronic illness and/or immunodeficiency are known to be a cause of impaired response to hepatitis B vaccine [Crosnier et al., 1981; Keet et al., 1992]; however, the immune response of patients with chronic liver disease to the hepatitis A vaccine has not been defined previously. This study was undertaken to evaluate the safety and immunogenicity of a hepatitis A vaccine in patients with chronic liver disease.

MATERIALS AND METHODS

Vaccines

Sixty patients, aged over 17 and diagnosed previously with chronic liver disease confirmed by liver aminotransferase levels more than twice the upper limit of normal laboratory assay on two specimens more than 6 months apart and/or positive liver biopsy, were enrolled into this open study. The study was approved by the ethics committee of Veterans General Hospital-Taipei and Department of Health, Executive Yuan, Republic of China. Informed consent was obtained from all participants. All vaccinees received a dose of inactivated hepatitis A vaccine [HM-175; SmithKline

Contract grant sponsor: Veterans General Hospital-Taipei; Contract Grant number VGH85-47.

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Accepted 28 January 1997

Beecham (SB) Biologicals, Rixensart, Belgium; 1440 enzyme-linked immunosorbent assay (ELISA) units (EL.U) of hepatitis A antigen in a volume of 1 ml/dose] at month 0, and then a booster dose in month 6. All vaccines were given into the deltoid muscle.

Follow-up and Laboratory Tests

Blood specimens were drawn from each vaccinee on days 0 and 15, and 1, 6 and 7 months after the first vaccination for quantitative antibodies to hepatitis A virus (anti-HAV) testing and liver aminotransferase measurement. Signs and symptoms were recorded on individual case report forms on the day of each vaccination and for the subsequent 7 days. Pre-vaccination blood samples for IgG anti-HAV screening were tested by a commercial radioimmunoassay kit (HAVAB®, Abbott Laboratories, Chicago, IL). Anti-HAV titers at all post-vaccination time-points were measured by ELISA (Enzymun-Boehringher kit, Mannheim, Germany) with an assay cut-off level of 33 mIU/ml. Hepatitis B surface antigen (HBsAg) (AUSRIA®, Abbott Laboratories, Chicago, IL), antibodies to HBsAg (AUSAB®, Abbott Laboratories), hepatitis B e antigen (HBeAg) and antibodies to HBeAg (Abbott HBe kit®, Abbott), and antibodies to hepatitis D antigen (anti-HDV) (Antidelta®, Abbott Laboratories) were measured by radioimmunoassay kits. Antibodies to hepatitis C virus (anti-HCV) (ABBOTT HCV II EIA®, Abbott Laboratories, Chicago, IL) were tested by commercially available ELISA kit. Serum alanine aminotransferase (ALT; normal values: ≤35 SF U/ml) and aspartate aminotransferase (AST; normal values: ≤40 SF U/ml) (Sigma Diagnostics Transaminase, St. Louis, MO) levels were measured by a photoelectric colorimeter.

Statistical Analysis

Statistical significance was determined by Mann-Whitney U test.

RESULTS

The study population consisted of 60 subjects without detectable anti-HAV (47 males and 13 females) between the ages of 17 and 47 years. All patients diagnosed previously with chronic liver disease (56 patients with chronic hepatitis B and four patients with chronic hepatitis C) were enrolled to receive two doses of inactivated hepatitis A vaccine. All subjects had ALT more than twice the normal laboratory value of the assay in two blood samples at least 6 months apart prior to vaccination. Thirteen patients also had liver biopsy with evidence of chronic hepatitis. One patient with chronic hepatitis B was also infected with hepatitis D. No one was alcoholic. All 60 patients received at least one dose of vaccine and were included in the analysis of reactogenicity. Of these, one patient with chronic hepatitis B was not included in the analysis of immunogenicity as result of initial anti-HAV seropositivity by repeat testing. Another subject with chronic hepatitis B was lost to follow-up for the second dose of vaccine. As shown in Figure 1, no significant change in serum liver aminotransferase levels was noted in any vaccinee at any time-point over the course of the study.

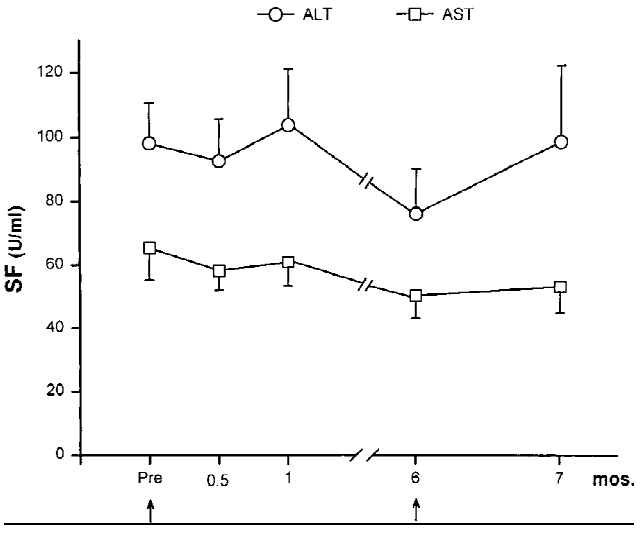

Fig. 1. Changes in serum liver enzyme levels in patients with chronic liver disease who received inactivated hepatitis A vaccine. Data are expressed as mean ± SEM. Arrows indicate administration of inactivated hepatitis A vaccine (1440 EL.U); ALT, alanine aminotransferase (normal values, ≤35 SF U/ml); AST, aspartate aminotransferase (normal values, ≤40 SF U/ml).

Reactogenicity data were based on symptom sheets returned after the administration of 119 doses of vaccine to 60 vaccinated subjects: 59.7% had experienced minor signs and symptoms (Fig. 2). The nature of the overall symptoms among those vaccinees was more local than general. The majority of symptoms, local or general, were mild in intensity and all resolved spontaneously. In comparison with the reported adverse effects of inactivated hepatitis A vaccine for healthy adults with same dose and schedule [Briem and Safary, 1994], our vaccinees tended to experience more local redness, swelling and malaise (Fig. 2). No serious adverse event was reported over the course of the study.

As shown in Figure 3, the anti-HAV response in initially seronegative vaccinees with chronic liver disease was 57.6% (34/59) on day 15 and reached 93.2% (55/59) 1 month after primary vaccination. In month 6 (at the time of booster vaccination), the seropositivity of anti-HAV decreased to 69.0% (40/58). One month after the booster vaccination, all vaccinees (100%, 58/58) became anti-HAV seropositive. To evaluate the persistence of vaccine-induced antibody, 43 vaccinees agreed to come back for a blood test 12 months after the first dose of vaccine. All were still anti-HAV seropositive. After the initial vaccination, the geometric mean titers (GMT) of anti-HAV in vaccine responders were 158, 264, 74, 1309, and 409 mIU/ml on day 15 and in months 1, 6, 7, and 12 respectively. No age or sex differences in anti-HAV response were found.

DISCUSSION

Inactivated hepatitis A vaccine is immunogenic and efficacious in preventing HAV infection in susceptible

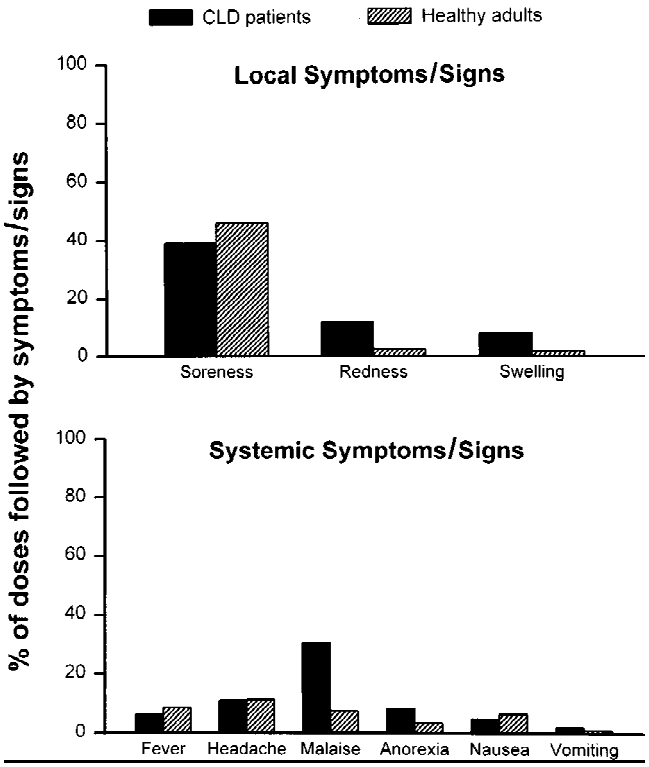

Fig. 2. Comparison of overall incidence of local and systemic symptoms and signs in patients with chronic liver disease (CLD) and healthy adults [Briem and Safary, 1994] who received the same dose and schedule of inactivated hepatitis A vaccine.

individuals [Andre et al., 1990; Briem and Safary, 1994; Lee et al., 1993; Weizberger et al., 1992]. The primary objective of the present open study was to evaluate the safety of inactivated hepatitis A vaccine containing 1440 EL. U hepatitis A antigen and using a 0, 6-month schedule given patients diagnosed previously with chronic liver disease. The reactogenicity analysis was derived from accounts of both solicited and unsolicited adverse events reported by the vaccinees during the course of the study. Diary cards were given to all subjects at the time of vaccination. A total of 119 symptom sheets were returned following the administration of 119 doses to 60 subjects (100% compliance). The incidence of reactogenicity was somewhat different from the previous report in healthy adult subjects vaccinated according to the same dose and schedule [Briem and Safary, 1994]. As shown in Figure 2, the incidence of malaise in our chronic liver diseased population was about five times that observed in healthy subjects, but all reported symptoms and signs were mild and resolved spontaneously within 3 days after vaccination.

Serum liver enzymes were measured at each time-point over the course of the study. All participants in the study had ALT more than twice the normal value of the assay in two blood samples at least 6 months apart prior to vaccination. No significant change in serum liver aminotransferase levels was noted in any vaccinee at any time-point. The vaccine did not exacerbate any pre-existing condition in any patient.

The vaccine evaluated during this study was shown to be safe in this population of patients with chronic liver disease. Although all subjects were seropositive following the booster vaccination, seroconversion rates were lower than in healthy subjects at all time-points before the booster vaccination (57.6% vs. 90% on day 15, 93.2% vs. 97% in month 1, 69.0% vs. 94% in month 6, and 100% vs. 100% in month 7, respectively) [Briem and Safary, 1994]. The geometric mean titers of anti-HAV antibody were also lower at all time-points than those observed in healthy subjects (158, 264, 74, and 1309 vs. 282, 589, 181, and 3629 mIU/ml on day 15 and at months 1, 6 and 7, respectively) [Briem and Safary, 1994]. The slower anti-HAV response and low GMT of anti-HAV among these patients was similar to our previous report of chronic HBV carriers who received a single dose of inactivated hepatitis A vaccine [Lee et al., 1996]. It has been reported that anti-HIV-positive men and hemophiliacs with low CD4 counts had lower seroconversion rates following hepatitis A vaccination [Hess et al., 1995; Zuckerman et al., 1996]. In addition, decreased inducer to cytotoxic/suppressor T-cell ratios were seen in patients with chronic HBV infection [Thomas et al., 1982]. Further study is necessary to determine whether the change of lymphocyte subpopulation in patients with chronic liver disease can reduce the immunogenicity to hepatitis A vaccine. Nevertheless, patients with chronic liver disease should probably receive a higher dose (i.e., 1440 EL.U; the regular dosage for healthy subjects in our country is 720 EL.U) and the classic two-dose schedule of hepatitis A vaccination for protection.

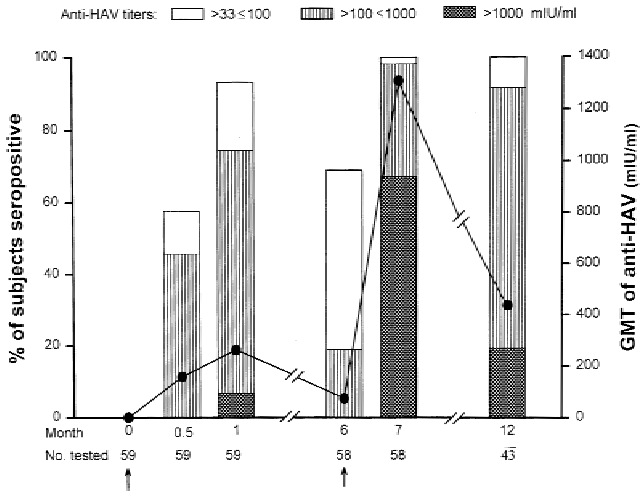

Fig. 3. Immunogenicity of inactivated hepatitis A vaccine in patients with chronic liver disease. Arrows indicate administration of inactivated hepatitis A vaccine (1440 EL.U); GMT, geometric mean titer.

ACKNOWLEDGMENTS

This study was supported by grants from Veterans General Hospital-Taipei (VGH85-47) and by Smith-Kline Beecham Biologicals, Rixensart, Belgium.

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